REMARKS

Claims 1 and 30-54 were pending in the instant application. In the Office action, the Examiner maintains his rejection of claim 1, and withdraws claims 30-54 from consideration.

The Examiner states as the reason for the withdrawal of claims 30-54 that these claims do not correspond to claims filed prior to the request for continued examination. Applicants contend that no new search would be required for claims 30-54, as searches performed for previous claims of the instant application would cover the subject matter of the new claims presented. Therefore, Applicants respectfully request that the Examiner reconsider these claims as imposing no undue burden on the Examiner, and that claims 34-50 be examined in light of the arguments presented below.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

For claim 1, the Examiner contends that the specification allegedly does not contain sufficient written description to enable the full scope of the invention as claimed. As Applicants discuss below, and as further validated by the Declaration of Dr. Adolfo Garcia-Sastre under 37 C.F.R. §1.132 (hereinafter "Garcia-Sastre Declaration") presented as Exhibit B, claims 1 and 30-54 are enabled by the specification as filed, and the rejection of these claims should not be maintained.

Claims 1 and 30-54 are drawn to recombinant influenza viruses comprising a heterologous sequence which encodes a tumor-associated antigen ("TAA") within the influenza viral genome, and vaccine formulations thereof. The specification teaches and it was routine in the art as of the filing date of the instant application to engineer influenza viruses to express a tumor antigen. According to the specification, sequences encoding a tumor specific antigen can be inserted into an open reading frame of a genomic segment of the influenza virus genome, preferably into a structural gene of the influenza virus, e.g., HA, NA (*see*, e.g., the instant specification at p. 15, lines 20-29). Alternatively, the tumor specific antigen may be placed in a bicistronic arrangement with an open reading frame of a genomic segment of the influenza virus genome (*see*, e.g., the instant specification at p. 9, line 32 to p. 10, line 4).

The instant specification teaches how to construct recombinant influenza viruses to express tumor specific antigens (*see* the specification at p. 8, line 26 to p. 10 line 4; p. 7, lines 1-16; p. 15, line 15 to p. 16, line 10). The specification provides an example of how a

recombinant influenza virus may be engineered to express a model tumor antigen, β-gal (*see* the specification at p. 15, line 15 to p. 22, line 12). The specification also provides the means to assay a recombinant influenza virus expressing a tumor-associated antigen to determine if that virus will elicit an immune response specific to that tumor antigen (*see* the specification at, *e.g.*, p. 18, line 8 to p. 19, line 11; p. 20, line 31 to p. 22, line 14). The instant specification meets the requirements of the first paragraph of 35 U.S.C § 112 by providing adequate enablement of the making and use of the invention as claimed.

As validation that the instant specification provides an enabling disclosure to construct and use recombinant influenza viruses containing tumor antigens, the Garcia-Sastre Declaration is offered for the Examiner's consideration. The Garcia-Sastre Declaration details how, using methods described in the specification of the instant application, a recombinant influenza virus may be constructed to express a tumor-associated antigen identified in the instant application, the HER-2/neu tumor associated antigen, E75[1], and assayed to determine the ability of said virus to stimulate an immune response (*see* the Garcia-Sastre Declaration at ¶¶ 4-5). This recombinant influenza virus expressing a tumor antigen within the influenza nonstructural (NS) region ("KIF-NS containing E75 virus") was successfully engineered using techniques outlined in the specification of the instant application.

The Garcia-Sastre Declaration describes experiments performed to assay the ability of the KIF-NS containing E75 virus to stimulate various components of the immune system. Specifically, the KIF-NS containing E75 virus was tested for:

(1) its ability to infect immune cells, e.g., immature dendritic cells (*see* the Garcia-Sastre Declaration at ¶ 7).;

(2) its ability to activate cellular immunity, e.g., induce interferon-gamma (IFN-γ; *see* the Garcia-Sastre Declaration at ¶ 8);

(3) its ability to activate cellular immunity specific to the tumor antigen (*see* the Garcia-Sastre Declaration at ¶ 9).; and

(4) its ability to induce lysis of tumor cells expressing the specific tumor antigen (*see* the Garcia-Sastre Declaration at ¶ 10).

The results of these experiments clearly indicate that the KIF-NS containing E75 virus, constructed using methods taught in the instant specification, stimulates an effective

immune response in each assay tested (*see* the Garcia-Sastre Declaration at ¶¶ 7-11). These studies confirm the ability of the recombinant viruses of the invention to generate a host immune response against TAAs, as illustrated and taught by the instant application in the successful generation of host immune response against β-gal by recombinant virus containing β-gal as a model tumor antigen.

The disclosure is objected to for failing to provide adequate guidance regarding the invention as claimed. It is alleged that a skilled artisan could not predict the nucleotide sequence necessary to generate an immune response against a given tumor antigen. This allegation is in error. As demonstrated in the Garcia-Sastre Declaration, the methods of the specification can be successfully applied using nucleotides encoding TAAs which can be identified by methods known in the art at the time of filing. The disclosure adequately describes the use of polynucleotides encoding TAAs for use in production of the recombinant influenza viruses of the invention. Structures of the tumor antigens (*e.g.*, the polynucleotide sequences of the tumor antigens) that can be used in accordance with the invention were known in the art as of the filing date of the instant application. Examples of specific TAAs are provided in the instant specification (*see* the specification at p. 8, Table 1). Human melanoma antigens, including melanocyte specific proteins (*e.g.*, MART-1, gp100, tyrosinase, and TRP-1), tumor-specific antigens (*e.g.*, MAGE-1, MAGE-3, BAGE, and GAGE), and tumor specific mutated antigens (*e.g.*, β-catenin, MUM-1, CDK4), had all been identified either through genetic or biochemical techniques as of 1996, well before the filing of the instant application. Additionally, the sequence of the epitopes derived from these tumor antigens that would be recognized by T lymphocytes had also been identified as of the filing date of the instant application.

In validation of the use of identified antigens as candidates for production of recombinant influenza viruses, the E75 antigen utilized in the studies described in the Garcia-Sastre Declaration is an epitope of the HER-2/neu protein, which is identified in Table 1 of the instant specification (*see* the Garcia-Sastre Declaration at ¶¶ 4-5, and the specification at p. 8, Table 1). As the experiments in the Garcia-Sastre Declaration demonstrate, antigens such as those disclosed in the specification can be engineered into the recombinant influenza viruses of the invention, using the methods of the invention, to stimulate an immune response to the identified antigen. The nucleotide sequence of the HER-2/neu TAA, which was used successfully in accordance with the methods of the invention, was known in the art prior to

[1] The HER-2/neu antigen is identified as an example of a tumor-associated antigen in the instant specification at

filing of the instant application. Thus, nucleotide sequences of tumor antigens that can be used in accordance with the invention were known in the art as of the filing of the instant application. Furthermore, methods for determining the structural motifs and molecular determinants required for recognition of tumor antigens by T lymphocytes had been established prior to the filing of the instant application, and were known in the art at that time.

The specification meets the legal test for enablement without necessitating undue experimentation. As stated by the Federal Circuit Court of Appeals (see *In re Wands*, 858 F2d 731 (Fed. Cir. 1988)):

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

It is alleged that the disclosure fails to support most polynucleotides encoding tumor associated antigens. This allegation is in error. The mere fact that there are many potential tumor antigens does not preclude enablement, provided that there is adequate disclosure in the specification and the art to permit the skilled artisan to practice the invention. This is true even if a considerable amount of laborious experimentation is required, although as the Garcia-Sastre Declaration makes clear, the engineering of a recombinant virus containing a tumor associated antigen using the methods of the specification can be accomplished without such laborious experimentation (*see* the Garcia-Sastre Declaration at ¶ 5). As demonstrated by the successful engineering of the KIF-NS containing E75 virus in the Garcia-Sastre Declaration (*see* the Garcia-Sastre Declaration at ¶ 5), any experimentation required to practice the invention of the instant application is indeed routine and the art provides adequate guidance regarding the identification of suitable tumor associated antigens and their epitopes which may be engineered into a recombinant influenza virus.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v.*

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p. 8, Table 1, under the heading "Non-melanoma antigens".

Telectronics Inc., 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, the specification need not describe and should preferably omit well known subject matter in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1367, 231 UPSQ 81 (Fed. Cir. 1986); *In re Hayes Microcomputer Products, Inc. Patent Litigation*, 982 F. 2d. 1527, 25 USPQ2d 1241 (Fed. Cir. 1992); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). These enablement rules preclude the need for the patent application to "set forth every minute detail regarding the invention" or to "disclose that which is already well known in the art" since the patent application speaks to those skilled in the art. *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991).

The Examiner's argument rests in part on the premise that the example provided in the instant specification, which discloses the making and use of recombinant influenza viruses containing β-gal as a heterologous antigen, fails to provide enabling support for claims to recombinant influenza viruses containing TAAs as heterologous antigens. This premise is clearly erroneous. As demonstrated by the Garcia-Sastre Declaration, β-gal is an appropriate model antigen for the methods of creating and assaying the recombinant influenza viruses of the invention. In the instant application, recombinant influenza virus containing β-gal as a heterologous antigen is constructed and tested for ability to elicit immune system activation against the β-gal antigen. In the Garcia-Sastre Declaration, the KIF-NS containing E75 virus is constructed and tested for ability to elicit immune system activation against the E75 antigen (*see* the Garcia-Sastre Declaration at ¶¶ 4-11). Construction of the recombinant influenza virus containing E75, which can activate the immune system to recognize the E75 tumor antigen, provides a direct example of the ability of the recombinant viruses created using the methods of the invention to activate an immune response against TAAs, just as recombinant influenza virus containing β-gal was used in the instant specification as an illustrative example for the ability of the recombinant influenza viruses created by the methods of the invention to activate an immune response against β-gal.

The Garcia-Sastre Declaration also demonstrates that the KIF-NS containing E75 virus successfully generated an immune response directed against the E75 epitope, indicating that the specification coupled with the knowledge of one skilled in the art can provide guidance to identify those sequences necessary to generate immune responses to tumor

associated antigens (*see* the Garcia-Sastre Declaration at ¶¶ 5-11). For a further discussion of this matter, the Examiner is invited to review the Applicants' Response filed June 26, 2001 in this case. Hence, the objection regarding the ability of a skilled artisan to practice the invention given the matter disclosed in the specification is in error.

It is alleged that the disclosure fails to include a clear, concise and reproducible method for obtaining tumor associated antigens with the desired activity commensurate in scope with that which is claimed. This allegation is in error. The teachings of the specification when combined with the knowledge in the art at the time of filing do in fact provide a clear, concise, reproducible method for obtaining a tumor associated antigen with the desired activity and engineering that antigen into a recombinant influenza viral vector. As demonstrated by the Garcia-Sastre Declaration, the disclosure is clear and concise in that it provides instruction as to how to engineer and test a recombinant influenza virus containing a TAA for ability to stimulate an immune response.

The disclosure is reproducible, in that the teachings of the specification were successfully applied to construct a recombinant influenza virus containing a tumor antigen. In the Garcia-Sastre Declaration, the methods described in the specification were used to engineer a TAA, the E75/KIF epitope, within a recombinant influenza virus, which has the desired activity commensurate in scope with what is claimed (*see* the Garcia-Sastre Declaration at ¶ 11). Claim 1 claims a recombinant influenza virus with a genomic region encoding a tumor antigen. The Garcia-Sastre Declaration confirms that the methods of the instant application provide a viable means to obtain a recombinant influenza virus with a genomic region encoding a tumor antigen as claimed (*see* the Garcia-Sastre Declaration at ¶¶ 4-5). Therefore, the method of the disclosure is both adequate and reproducible to obtain the desired result.

It is alleged that the prior art is unpredictable. This allegation is in error. As discussed above, the prior art teaches the identification of tumor associated antigens, the identification of peptide sequences derived from tumor antigens necessary to elicit a cellular immune response, and methods to identify new tumor associated antigens. Further, as seen in the Garcia-Sastre Declaration, the methods of the specification combined with prior art knowledge of TAAs can produce the recombinant influenza viruses of the invention in a routine and predictable manner, as evidenced by the creation of the KIF-NS containing E75 virus which effectively stimulates an immune response against the E75 antigen (*see* the Garcia-Sastre Declaration at ¶¶ 4-11). Construction of the recombinant influenza viruses of the Garcia-Sastre Declaration, using the methods of the Example provided in the instant

application for construction of a recombinant influenza virus containing the model tumor antigen β-gal, also validates the use of β-gal as an appropriate model tumor antigen. In the studies of the Garcia-Sastre Declaration, the KIF-NS containing E75 virus was shown to induce an immune response against E75, a human tumor antigen, just as the β-gal containing influenza virus used as a model in the instant application was shown to induce an immune response against β-gal. The recombinant virus of the Garcia-Sastre Declaration was successfully constructed using guidance from the prior art relating to immunogenic tumor antigens (*see* the Garcia-Sastre Declaration at ¶ 5). Hence the art is not unpredictable.

It is alleged that the scope of enablement provided by the disclosure of the invention does not reasonably correlate to the scope of the claims. This allegation is in error. The specification of the instant application is sufficient to teach those of ordinary skill in the art how to make and use the invention as broadly as is claimed. As stated in the Garcia-Sastre Declaration, the teachings provided in the specification can be used to engineer a recombinant influenza virus expressing a tumor antigen, KIF-NS, containing the HER-2 E75 antigen. This recombinant influenza virus is a potent inducer of immune cell response to the HER-2 E75 TAA, indicating that a vaccine produced which has as a component the KIF-NS containing E75 virus made by the teachings of the invention may be an effective anti-tumor agent (*see* the Garcia-Sastre Declaration at ¶¶ 4-11).

In view of the foregoing, Applicants assert that the specification fully describes the claimed invention, and coupled with the state of the art at the time the application was first filed, one skilled in the art can make and use the claimed invention without having to resort to undue experimentation. Thus, one of skill in the art, as of the filing date of the instant application, would have known how to make and use a recombinant influenza virus having a genome comprising a heterologous sequence encoding a tumor antigen.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing remarks. The claims are believed to be free of the art and patentable. Withdrawal of all the rejections and objections and an allowance are earnestly sought.

If any issues remain, the Examiner is requested to telephone the undersigned.

Respectfully submitted,

by: Jacqueline Benn
Reg No. 43,492

Date: July 14, 2003

By: Laura A. Coruzzi 30,742
Laura A. Coruzzi Reg. No.

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, NY 10036-2711
Tel. (212) 790-9090